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Contact allergy to preservatives. Analysis of IVDK¹ data 1996 - 2009

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Abstract

Objective: To examine the frequency of sensitization to preservatives, including time trends.

Methods: Retrospective analysis of data on patch testing preservatives contained in the standard series and special series collected by the IVDK 1996-2009.

Results: Some 120,000 and 80,000 patients were tested with the baseline and the preservative series, respectively. Sensitization frequencies of the standard series allergens all ranged above 1%: Methylidibromoglutaronitrile (MDBGN) 2.36 – 4.5%, methyl(chloro)isothiazolinone (MCI/MI) 2.22%, formaldehyde 1.54%, paraben mix 1.33% and Bronopol™ 1.25%. Regarding the special preservative series, 1.54% reacted positive to methylisothiazolinone (MI), and less than 1% to the other preservatives. Concomitant reactions to formaldehyde in formaldehyde releasers ranged from 15% to almost 50%, and 67% of MI positives reacted to MCI/MI. As indicated by the MOAHLFA-index, sensitization to MI, iodopropinylbutyl carbamate (IPBC), and quaternium 15 was associated more often with occupational dermatitis, whereas sensitization to imidazolidinyl urea and diazolidinyl urea was associated with face dermatitis, indicating cosmetic exposure. Epidemiologically relevant decreases (>10%) were seen in chloroacetamide, benzyl alcohol and MDBGN. Epidemiologically relevant increases were noted in IPBC, sodium benzoate, and MI.

Conclusion: Preservatives are still important contact allergens. The introduction of new preservatives should consider the specific characteristics of occupational and of non-occupational (cosmetic, household) exposure, and preventive measures should aim equally at both areas.

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Key words

Contact allergy, preservatives, time-trend, cosmetics

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Preservatives have been recognized since long as important skin sensitizers [1]. The first standard series proposed by Bonnevie in 1939 already contained formaldehyde (as 'formalin') [2]. In the sixties of the last century, the ICDRG tested formaldehyde and the paraben mix [3]. During the last decades, a considerable number of newly developed preservatives such as isothiazolinones, formaldehyde releasers or methyldibromo glutaronitrile were found to be sensitizers and were added to the standard series or to special patch test series. The impact of sensitization to preservatives has been substantiated by analyses of larger patch test populations, time trends included, on national [4, 5, 6] North American [7, 8, 9] and European levels [10, 11]. More recently, Jong et al and Thyssen et al reported on preservative allergies in the UK and Denmark, respectively [12, 13]. We were interested in the frequency of allergies to preservatives in central Europe, and therefore analysed data of the IVDK from 1996 to 2009.

Methods:

The Information Network of Departments of Dermatology (IVDK, www.ivdk.org), a contact allergy surveillance network in Germany, Switzerland and Austria, has been described elsewhere [14]. Briefly, results of all patients patch tested in the participating departments are electronically recorded, along with important demographic and clinical data. The diagnostic procedure follows international guidelines [15], further refined by the German Contact Dermatitis Research Group (DKG) [16], of which all IVDK participants are members. All data is transmitted to the data centre in Göttingen in an anonymous format twice yearly, where it is checked and, if satisfying internal quality control criteria [17], analysed according to international guidelines [18].

For the present analysis, data of all patients patch tested with the preservatives listed in table 1 between 01/1996 and 12/2009 were included. Results with substances tested in the baseline series and with those tested in special series are presented in separate sections of table 1. Some allergens were not tested during the whole period, but during a limited period only: methyldibromo glutaronitrile (MDBGN) 0.2 (as Euxyl K 400 containing MDBGN 0.2% and phenoxyethanol 0.8%) between 1998 and 2004 and again 2009 (MDBGN 0.2% only) in the baseline series, and in 2005 in the monitor series (together with the baseline series). Iodopropinylbutyl carbamate (IPBC) was tested since 2003 in special series, and during 2004 additionally in the monitor series. Bronopol® (2-bromo-2-nitro-1,3-propandiol) was tested 2004/5 both in the monitor series and special series (in those departments not using the monitor series), and, since 2006, in the baseline series. Polyhexamethylene biguanide (PHMB) (delivered by Arch UK Biocides Ltd, Manchester) was tested in two concentrations (2.5% and 5%) in consecutive patients taking part in two special studies, in 1998 and in the second half of 2005 [19, 20]. Methylisothiazolinone (MI) was tested in the monitor series in 2005, sporadically in 2006 and 2007, and regularly, since 2008, in the preservative series and the industrial biocide series

Patch test preparations (except PHMB) were provided by Almirall-Hermal/Trolab, Reinbek, Germany. Weak ('+') to strong ('+++') positive patch test reactions on the 3rd day after application of the test or, if this was not read, after the 4th day were aggregated as outcome 'positive' and contrasted to non-positive (non-allergic) reactions, comprising negative, doubtful and irritant reactions.

Frequencies of sensitization (as % of patients tested) were calculated both as crude proportions and as proportions standardized for sex and age [21], the latter accompanied by the 95% confidence interval (95% CI). Patch test results were generally analysed regarding (i) the total period, and (ii) stratified for sex. Moreover, time trend analyses were performed based on the bi-annual frequencies of sensitization, standardized for sex and age. A time trend was statistically tested by using the Wald χ^2 statistic of a logistic regression analysis, thereby adjusting for sex and age (dichotomised as age < 40 vs. age 40 and above). The reaction index (RI), relating the number of allergic reactions to the number of doubtful or irritant reactions [22, 23], and the positivity ratio (PR), relating the frequency of + reactions to the total number of allergic reactions [24], were calculated as parameters to assess the patch test preparation. Patients reacting positive were characterized by the MOAHLFA Index [21] (Tab 5). For data management and analysis, the statistical software package SAS (version 9.2, SAS Institute, Cary, NC, USA) was used.

Results

The number of patients tested and the frequency of sensitization (n and % standardized for sex and age) in the total population, in women and men are shown in table 1. Due to selected testing with special series, frequencies of sensitization found in allergens of the standard series and in allergens tested in special series are not directly comparable. Sensitization frequencies of the standard series allergens all ranged above 1%. Their inclusion in the baseline series is thus well justified [15]. In view of (i) an overall frequency of 1.54% (95%CI: 1.32 – 1.77) and (ii) a significant increase of sensitisation prevalence, MI should be evaluated regarding the inclusion into the standard series. All the other preservatives may remain in their specific series, as they do not reach the threshold of 1% even if tested in an aimed fashion. Sensitization to the following allergens was significantly more frequent in men: Paraben-Mix, sodium benzoate, and sorbic acid, whereas sensitization to chloroacetamide, diazolidinyl urea, quaternium 15, and imidazolidinyl urea was more frequent in women (table 1).

Concomitant reactions between formaldehyde and formaldehyde releasers and between MCI/MI and MI are shown in table 2 and table 3. About half of the DMDM hydantoin and quaternium 15 positive patients also reacted to formaldehyde, while less (up to 20%) of those reacting to the diazolidinyl urea and imidazolidinyl urea reacted to formaldehyde. Only 5% of Bronopol® positive patients reacted to formaldehyde, too. Regarding the isothiazolinones considered here, 40% of MCI/MI positive patients also reacted to MI, whereas almost 70% of patients positive to MI also reacted to MCI/MI.

The RI and PR are presented in table 4. Allergens are assigned to three classes according to their RI. In general, a positive RI goes along with a good PR (<80%), except for imidazolidinyl urea. In contrast, substances of group III, with a RI < 0.0, differ significantly from substances of group I and group II, all with an unfavourable PR (the upper 95% CI markedly above 80%), among them the paraben mix, a baseline series allergen. Substances of this group must be regarded as 'problematic' patch test preparations [24, 25, 26], although stronger (++/+++) unequivocal allergic reactions may rarely occur. This can be illustrated by the paraben-mix: Only 266 out of 121,247 patients tested (0.2%) reacted with a strong or extreme positive reaction (++ or +++).

It is noteworthy that the allergens found more often in men (paraben-mix, sodium benzoate, sorbic acid) are characterized by a low RI and a high PR indicating a certain irritant potential, possibly giving rise to some false positive reactions (see discussion). The MOAHLFA-Index of the population reacting positive to the allergens is presented in table 5. Distinct patterns are discernible. There are allergens associated with suspected occupational dermatitis (together with hand dermatitis), at the top MI, phenoxyethanol, quaternium 15 and IPBC. In contrast, sensitization to diazolidinyl urea and imidazolidinyl urea are characterized by a high proportion of face dermatitis, suggestive of causal cosmetic exposure [27]. Finally, sensitization to a number of allergens is associated with leg dermatitis, namely Bronopol ® chlorhexidine, << parabens, triclosan, < chloracetamide and << benzyl alcohol.

Analyses of time trends (fig. 1 and 2a to 2c) reveal decreases of sensitization prevalences in most of the biocides which were statistically significant, but may be considered epidemiologically relevant (decrease >10% / 2 years) only in chloroacetamide (OR 0.88; CI: 0.85 - 0.91), benzyl alcohol (OR: 0.87; CI: 0.82 - 0.92), and MDBGN 0.2% (OR 0.89; CI: 0.87 - 0.91) as well as MDBGN 0.3% (OR: 0.88; CI 0.86 - 0.90) – all odds ratios are estimates of the effect per 2 years (regarding MDBGN: in those years the allergen was tested). No significant changes over time were seen in case of Bronopol ®, imidazolidinyl urea and phenoxyethanol. In contrast, a slight, but significant increase was seen in quaternium 15, and epidemiologically relevant increases (> 10% / 2 years) were noted in IPBC (OR: 1.12; CI 1.02 – 1.24), sodium benzoate (OR 1.19; CI 1.14 – 1.25), and MI (OR: 1.22; CI: 1.07 – 1.40). If for MI the initial period (1996/7), during which it was tested in 563 patients, is omitted, the OR estimate for trend based on the last 6 years amounts to 1.55 (95% CI: 1.25 – 1.93).

Discussion

For several reasons the study of the frequency of sensitization to specific allergens might be important:

- Frequent sensitisers should be subject to prevention and (regulatory) intervention. A sensitivity rate $\leq 1\%$ in patch test populations has been regarded as acceptable. If it exceeded 2% there would be concerns, and if it exceeded 3% there would usually be a problem [10]. More recently, this view has been put into

perspective emphasizing that a sensitization frequency of 0.6% observed in patients would translate to 1/1000 in the general population, according to a “medium” assumption. This was called a “concentrated epidemic” [28].

- Monitoring trends of sensitization is the “cornerstone objective” [29] in a surveillance system of contact allergies. Increasing trends must be considered as ‘sentinel health events’ prompting further analysis and subsequent preventive action [30]. Likewise, trends levelling off and not decreasing after an intervention indicate its (partial) failure [31]. In contrast, significantly and relevantly decreasing trends may prove interventions to have been sufficiently successful [32, 33, 34].

- Sensitization frequencies in unselected, consecutive patients continually above 1% qualify the allergen to be included in the baseline series [15]. Lower frequencies would probably make them a candidate for special series, such as the preservative series, if other considerations would not support inclusion in the baseline series.

Preservatives of the baseline series, MDBGN, MCI/MI, formaldehyde, parabens and Bronopol® (the latter included more recently) all exceeded the threshold of 1% (table 1). The other preservatives remained below this level, except MI, which should be evaluated regarding the inclusion into the standard series. On the other extreme, there are preservatives with a very low sensitization rate despite frequent use [35, 36]. Phenoxyethanol could be regarded as an extremely rare allergen, if as an allergen at all (table 1) [37, 38, 39, 4], a view further supported by an ‘unfavourable’ reaction profile (table 4).

With regard to time trends, epidemiologically relevant decreases (>10%) were seen in chloroacetamide, benzyl alcohol, and, more importantly, in MDBGN. Epidemiologically relevant increases (> 10%) were noted in IPBC, sodium benzoate, and MI.

However, further data from epidemiological surveillance may help elucidating the background of these statistical figures. The reaction profile of patch test preparations expressed by the RI and the PR will support the notion of some substances being unequivocally allergenic (e.g. MDBGN or MCI/MI), but, on the other hand, may unveil a number of allergens, those with a negative RI and a high PR (table 4), as probably causing false positive reactions in a substantial proportion [25, 26]. The parabens (RI: -0.22, PR: 84.8%) may serve as an example. 1.3% of patients tested reacted to parabens (table 1), but one should realize that only 266 out of 121,247 patients tested (0.2%) reacted with a stronger, unequivocally allergic reaction. Instead, a larger part of ‘positive’ reactions to parabens may be explained by the irritant potential of parabens [12], supported by frequent concomitant reactions to low concentrations (0.25%) of the irritant sodium lauryl sulphate (SLS) [25]. The difference in paraben positivity between males and females could be due to different irritability of the sexes. The significantly higher positivity in men (1.7 vs. 1.2%) (table 1), also observed by others [12, 13], cannot reasonably be explained by a sex-specific exposure to parabens, which are almost exclusively used in cosmetics. In former studies we have shown that the male sex was a weak

but significant risk factor, both with regard to reactions to SLS [40] as to cocamidopropyl betaine, also known for its irritability in patch testing [41]. In addition, men reacted significantly more often to sorbic acid and sodium benzoate (table 1), again patch test preparations with an unfavourable reaction profile (table 4). Thus an increased propensity of the male sex to react 'allergic' to irritant patch test preparations – the parabens belonging to this group - is obvious [42].

Further insights may be given by another epidemiological data, the MOAHLFA-Index (table 5). A number of sensitization is obviously associated with occupational dermatitis ('O'), where often the hands ('H') are affected (table 5) [43], among them MI, phenoxyethanol, MCI/MI, IPBC and formaldehyde (and certain releasers). However, a selection bias may act as a confounder, as MI, phenoxyethanol and IPBC were included in the industrial biocide and MWF-series predominantly tested in male workers. In the case of formaldehyde, a well known occupational allergen [44], the association is very plausible, as it is not used in cosmetics at all. Quaternium 15 and DMDM hydantoin, very rarely (~ 0.2%) used in leave-on cosmetics [36], may simply follow formaldehyde's wake with regard to the 'O' association, owing to frequent concomitant reactions to formaldehyde (table 2) [45]. Others, namely imidazolidinyl urea and diazolidinyl urea, more weakly associated with formaldehyde allergy (table 2) and considered as sensitizing molecules of their own right [46], are associated with face dermatitis which is more suggestive of a causal exposure to cosmetics [27]. Finally, leg dermatitis, a well known risk factor for sensitization to even weak allergens [47], was found to be associated with allergens figuring at the lower ranks of the statistics of sensitization (table 1).

However, it should be stressed that the characteristics of the MOAHLFA-index will only give hints regarding causal exposures. For example, IPBC allergy shows, at first, a typical 'occupational pattern' (male: 46%, occupational:31%, hands: 46%). In Denmark, men were significantly more often sensitized to IPBC [13] (see also table 1). In line with this observation is the wide industrial application, e.g in cutting fluids and paints [48, 49]. On the other hand, IPBC is increasingly used in cosmetics [48, 50]. Is it plausible that the sensitization frequency and its increase during the last years could be at least partly caused by cosmetics? According to a quantitative risk assessment (QRA) taking into account the sensitizing potency of IPBC and exposure through different product types the "typical exposure" does not exceed the "acceptable exposure", except only for the maximum permitted level in non aerosol-deodorants [51]. Although the QRA approach has been critically commented on and has still to prove its validity [52], further data on exposure indicate a rather minor role of cosmetics concerning IPBC sensitisation: During the period 2006 to 2009, preservative labelling on cosmetic products was registered by the CVUA Karlsruhe. IPBC was present in 47/1261 (3.7%) rinse-off and 93/4133 (2.3%) leave-on products [36]. Even more, IPBC was not present in any of the deodorants. According to a source from North America, IPBC was present in 5.5% of shampoos [53]. Lacking a probable alternative explanation, notwithstanding single case reports [54], our first interpretation of IPBC being a sensitizer substantially through occupational exposure thus seems justified [55, 56, 57, 58].

A similar, but not identical, reasoning may apply to the case of MI. With 1.5% positives, MI seems to become an important allergen, and has seen a significant increase during the last years. Similar figures from testing MI in unselected patients (1.4%, 147/10,821 and 1.5%, 37/2536, respectively) were recently reported from Finland [59] and Denmark [60]. In the Danish study occupational dermatitis, hand dermatitis and older age were significantly overrepresented in MI-positives [60]. In 24/37 the exposure could be traced. 7 MI positives were exposed to cosmetics containing MI (2 leave-on and 5 rinse-off) [60]. Occupational sensitization to MI has been described earlier [61, 62], and recently, 7 cases patch test positive to MI were described. 6 of these patient suffered of (peri-)anal dermatitis and had used intimate hygiene products containing MI [63].

In our analysis, MI ranks first with regard to occupational dermatitis, combined with frequent hand dermatitis (table 5). It is mainly used in paints/lacquers, and many other industrial applications, but also in toiletries and cosmetics [35, 64]. However, only 12/1261 (0.95%) of rinse-off and 30/4133 (0.73%) leave-on cosmetics (none was a deodorant) contained MI, according to the CVUA-statistics 2006-2009 quoted before [36]. In 2003 the SCCNFP and in 2010 the Cosmetic Ingredient Review Expert Panel regarded MI as “safe” (with regard to induction), when used at concentrations of 100ppm in cosmetics [65, 64]

Although there are several case reports of sensitization to MI probably independent of, or prior to, sensitization to MCI/MI [61, 62, 66, 67, 63], the question remains how large this proportion is in larger patch studies. An unknown proportion of reactions to MI could be due to previous sensitization to MCI/MI through various sources (cosmetic and non-cosmetic), and possibly many years ago, as cross reactions between MI and MCI/MI might suggest [60]. In the study by Lundov et al. [60], 41% of MI-positives reacted also to MCI/MI (a proportion also reported from Leuven [63]). In the Finnish study, 66% of MI positives reacted to MCI/MI, and 50% of MCI/MI positives to MI [59]. In our study MCI/MI positives reacted to MI in almost 40%. An even higher proportion of MI positives reacted to MCI/MI (67%), an “asymmetrical” cross-reaction pattern we had observed earlier, explained by different potencies of the allergens involved [68]. In view of the relatively low sensitizing potency of MI, and the very low exposure through rinse-off products, MI-positive cases exposed to MI-containing rinse-off products might have been primarily sensitized by MCI [60], as MCI is a much more potent sensitizer [69] and exposure to MCI is substantially more frequent [35, 36]. Leaving apart the prevailing occupational exposure to MCI/MI, almost 8% of rinse-off products, and 2.2% (63/421) of leave-on products, mainly sun protective preparations (63/91), contained MCI/MI according to the CVUA statistics [36]. However, primary sensitization to MI seems more obvious in the six cases with (peri-)anal dermatitis exposed to MI-containing moist toilet paper [63]. Like leg dermatitis, perianal eczema can be regarded as a *locus minoris resistentiae* with regard to sensitization [70, 71]. However, these particular cases do certainly not support MI being the “emerging allergen in cosmetics” [63]. Apparently, the typical use conditions of moist toilet papers render these not representative for leave-on products, and certainly not for rinse-off cosmetics. Nevertheless, the fact remains that allergic reactions to MI are increasing. Whether this is due to increasing exposure to MCI in cosmetic applications, to increasing exposure to MI in industrial

applications (e.g. paints), or to the yet rather rare exposure of MI alone in cosmetics, cannot definitely be decided. To effectively target preventive action, it is of utmost importance to identify culprit exposures.

One allergen stood out, namely MDBGN, as it saw a significant decrease of sensitization during the last years, as shown in our (fig. 1) as in other studies [34, 12, 13]. Introduced as a new preservative in 1984, a larger series of allergies to MDBGN (n=36) as well as an increase in sensitization (from 0,7% in 1990 to 2.1% in 1994) have been observed and published first in Germany [38, 72]. Already in 1989, one of six “experts on contact allergy” (the German dermatologist Hellmut Ippen) proposed MDBGN to be named “allergen of the year” [73]. During the following decade further data were published showing high and increasing rates of sensitization [39, 74, 75, 76, 6]. Finally, MDBGN was banned from being used in leave-on products in 2003, brought into force in 2005 [77] and, following a recommendation of the SCCP in 2005 [78], banned in rinse-off products in 2007 as well, brought into force 2008 [79]. A significant decline ensued clearly visible in our (fig. 1) as in other data already in 2004/2005 [34, 12, 13]. From an epidemiological point of view, rinse-off products, banned for MDBGN in 2007, appear to have played a minor role in sensitization to MDBGN. Recently, it was shown that MDBGN can probably be used safely in rinse-off cosmetics at concentrations of about 50ppm, even in individuals already sensitized to MDBGN [80], a concentration unlikely to cause new primary sensitization through rinse-off products. Following the total ban, MDBGN is virtually excluded from the market of cosmetics [36]. The high prevalence of sensitization still observed is probably due to former exposure and/or to continued occupational, at least non-cosmetic, exposure.

Conclusion:

The increase of sensitization to IPBC, MI and sodium benzoate could be caused by an increased use in occupational products, or, paradoxically, reflect the efforts of the cosmetic industry to use alternatives deemed less allergenic, possibly referring to preclinical potency classification and quantitative risk assessments [51]. Observation in humans, however, shows that (i) substitution of (biologically active) preservatives is a somehow problematic endeavour [51, 81, 82], which de Groot sarcastically referred to as „van de regen in de drup“ (out of the frying pan into the fire) [83, 84], and that (ii) regulations as well as use of a chemical based on animal tests (only) need to be controlled by epidemiological/clinical surveillance, which has been made very clear by T. Menné [85].

Before relying on the sheer frequencies of sensitization (table 1) as a basis of risk assessment and subsequent substitution of allergenic substances (this consideration would apply to industry as to dermatologists), the interfering factors (population characteristics or diagnostic weakness) as well as exposure should be considered. A measure to improve the safety of cosmetics should for instance take into account potentially harmful occupational exposures or defined, small subpopulations at greater risk, and vice versa. This neglected aspect may partly explain the unchanged impact of preservatives on contact allergy today.

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Table 1: Frequency of sensitization to preservatives in the total patch test population, standardized for sex and age, and further stratified for male and female patients, standardized for age. Frequencies of sensitization found in allergens of the standard series and in allergens tested in special series are not comparable directly, as in the latter frequencies are often found to be higher [86].

		Total patch test population					men					women				
allergen	c o n c	n tes ted	n p o s	% s t d	95% CI	n tes ted	n p o s	% s t d	95% CI	n tes ted	n p o s	% s t d	95 % CI			
Tested in the baseline series																
Methyldibromoglu taronitrile	0 , 3	53 54 5	2 6 9 5	4 .5 5 0	4 .3 6 3	4 .6 8	20 41 4	1 1 1 9	4 .8 2	4 .5 2	5 1 1	33 13 1	1 5 7 6	4 .3 3	4 .1 1	4 .5 5
Methyldibromoglu taronitrile+ PE	1	60 93 6	2 5 9 3	3 .8 9	3 .7 4	4 .0 5	23 02 7	1 0 4 2	4 .1 1	3 .8 5	4 3 6	37 90 9	1 5 5 1	3 .7 8	3 .5 9	3 .9 7
Methyldibromoglu taronitrile	0 , 2	13 36 9	3 7 1	2 .3 6	2 .1 0	2 .6 2	49 81	1 5 4	2 .6 1	2 .1 6	3 0 5	83 88	2 1 7	2 .2 3	1 .9 0	2 .5 5
(Chloro)- Methylisothiazolin one (MCI/MI)	0 , 0 1	12 11 36	2 8 0 5	2 .2 2 2	2 .1 3	2 .3 0	45 70 0	1 0 7 8	2 .2 3	2 .0 9	2 3 7	75 43 6	1 7 2 7	2 .2 1	2 .1 0	2 .3 2
Formaldehyde	1	12 15 58	1 9 0 8	1 .5 4	1 .4 7	1 .6 2	45 83 2	7 0 5	1 .4 3	1 .3 2	1 5 4	75 72 6	1 2 0 3	1 .6 1	1 .5 1	1 .7 0

Paraben-Mix	1 6 . 0	12 12 47	1 7 5 2	1 . 3 3	1 . 2 6	1 . 3 9	45 74 1	8 0 3	1 . 6 6	1 . 5 4	1 . 7 9	75 50 6	9 4 9	1 . 1 5	1 . 0 7	1 . 2 2
Bronopol	0 , 5	42 88 2	6 1 3	1 . 2 5	1 . 1 4	1 . 3 5	16 39 6	2 6 8	1 . 3 7	1 . 1 9	1 . 5 5	26 48 6	3 4 5	1 . 1 8	1 . 0 4	1 . 3 2
Tested in special series																
Methylisothiazolin one	0 , 0 5	13 43 3	2 1 5	1 . 5 4	1 . 3 2	1 . 7 7	51 74	1 0 3	1 . 9 1	1 . 5 1	2 . 3 1	82 59	1 1 2	1 . 3 4	1 . 0 7	1 . 6 1
Iodopropinylbutyl carbamate	0 , 2	40 77 2	3 8 9	0 . 8 8	0 . 7 9	0 . 9 8	15 91 4	1 8 0	1 . 0 3	0 . 8 7	1 . 1 9	24 85 8	2 0 9	0 . 8 0	0 . 6 9	0 . 9 2
Polyhexamethyle ne biguanide-HCl	5	32 07	3 0	0 . 8 8	0 . 5 4	1 . 2 3	12 47	1 1	0 . 7 8	0 . 2 8	1 . 2 9	19 60	1 9	0 . 9 4	0 . 4 8	1 . 4 0
Chloracetamide	0 , 2	80 82 4	7 1 7	0 . 7 9	0 . 7 3	0 . 8 5	30 72 5	2 0 4	0 . 5 6	0 . 4 8	0 . 6 4	50 09 9	5 1 3	0 . 9 2	0 . 8 3	1 . 0 0
Diazolidinyl urea	2	78 71 1	5 8 7	0 . 7 1	0 . 6 5	0 . 7 7	29 38 7	1 9 4	0 . 5 6	0 . 4 7	0 . 6 4	49 32 4	3 9 3	0 . 8 0	0 . 7 1	0 . 8 8
Sodium benzoate	5	79 04 6	5 1 2	0 . 6 9	0 . 6 2	0 . 7 5	29 20 9	2 5 6	0 . 8 9	0 . 7 7	1 . 0 0	49 83 7	2 5 6	0 . 5 8	0 . 5 1	0 . 6 6

Quaternium 15	1	79 74 5	5 1 0	0 .6 6	0 .7 2	29 71 9	1 3 7	0 .4 4	0 .3 6	0 .5 2	50 02 6	3 7 3	0 .7 7	0 .6 9	0 .8 6
Imidazolidinyl urea	2	78 67 0	4 7 9	0 .6 6	0 .5 4	29 28 5	1 6 1	0 .4 9	0 .4 1	0 .5 7	49 38 5	3 1 8	0 .6 5	0 .5 8	0 .7 3
Sorbic acid	2	77 70 8	5 1 9	0 .5 8	0 .5 2	28 83 1	2 9 3	0 .8 6	0 .7 5	0 .9 6	48 87 7	2 2 6	0 .4 3	0 .3 7	0 .4 8
Polyhexamethyle ne biguanide-HCl	2 , 5	88 48	6 0	0 .5 8	0 .4 3	32 07	2 8	0 .7 1	0 .4 4	0 .9 7	56 41	3 2	0 .5 2	0 .3 3	0 .7 0
DMDM Hydantoin	2	78 26 6	3 8 8	0 .4 9	0 .4 4	28 92 9	1 4 8	0 .4 6	0 .3 8	0 .5 4	49 33 7	2 4 0	0 .5 1	0 .4 4	0 .5 8
Chlorhexidin digluconate	0 , 5	80 90 6	3 6 8	0 .4 2	0 .3 8	29 72 9	1 7 0	0 .5 1	0 .4 3	0 .6 0	51 17 7	1 9 8	0 .3 7	0 .3 2	0 .4 3
Triclosan	2	79 03 3	2 5 4	0 .2 9	0 .2 5	29 21 8	8 7	0 .2 7	0 .2 1	0 .3 3	49 81 5	1 6 7	0 .3 0	0 .2 6	0 .3 5
Benzyl alcohol	1	79 77 0	2 5 8	0 .2 8	0 .2 5	29 51 9	6 4	0 .1 8	0 .1 3	0 .2 3	50 25 1	1 9 4	0 .3 4	0 .2 9	0 .3 9

2-Phenoxyethanol	1	69 32	2 0	0 . 2 4	0 . 1 2	0 . 3 6	41 90	1 4	0 . 3 2	0 . 1 5	0 . 4 9	27 42	6	0 . 2 0	0 . 0 4	0 . 3 6
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Conc (%): Concentration in petrolatum, except MCI/MI, Formaldehyde and DMDM Hydantoin (in aqua). % stand: frequency of positives standadized for sex and age. 95%CI: 95% confidence interval

Table 2: Concomitant reactions between formaldehyde and -releasers

	Releaser positives reacting to formaldehyde		Formaldehyde positives reacting to releaser	
	n	%	n	%
Sensitization to				
DMDM	172/353	48.7	172/1168	14.7
Hydantoin				
Quaternium 15	217/466	46.6	217/1202	18.1
Diazolidinyl Urea	108/560	19.3	108/1169	9.2
Imidazolidinyl Urea	71/457	15.5	71/1170	6.1
Bronopol	69/1252	5.5	69/1416	4.9

Table 3: Cross Reactions between MCI/MI and MI

	n	%
MCI/MI positives reacting to MI	134/339	39.5
MI positives reacting to MCI/MI	134/199	67.3

MCI/MI: methylchlorisothiazolinone/ methylisothiazolinone (4:1) 100ppm in petr

MI: methylisothiazolinone 500 ppm in petr.

Table 4: Reaction Index (RI) and Positivity Ratio (PR) of preservative patch test preparations, accompanied by the 95% Confidence Interval (95% CI), sorted by RI in decreasing order

allergen	RI	(95% CI)	PR	(95% CI)
I. RI $\geq$ 0.20 (lower 95% CI)				
(Chloro)-Methylisothiazolinone (MCI/MI)	0.50	(0.47 - 0.53)	66.2	(64.4 - 67.9)
Methyldibromoglutaronitrile+ PE 1.0%	0.43	(0.40 - 0.46)	70.2	(68.4 - 71.9)
Methylisothiazolinone	0.43	(0.33 - 0.53)	61.4	(54.9 - 67.9)
Chloracetamide	0.37	(0.31 - 0.43)	61.8	(58.2 - 65.3)
Quaternium 15	0.33	(0.26 - 0.39)	67.1	(63.0 - 71.1)
Imidazolidinyl urea	0.28	(0.21 - 0.35)	82.5	(79.1 - 85.9)
Diazolidinyl urea	0.26	(0.20 - 0.33)	77.9	(74.5 - 81.2)
II. 0.0 < RI < 0.20 (lower 95% CI)				
Methyldibromoglutaronitrile 0.2%	0.25	(0.19 - 0.32)	78.3	(74.9 - 81.7)
Formaldehyde	0.20	(0.17 - 0.24)	75.2	(73.3 - 77.1)
Methyldibromoglutaronitrile 0.3%	0.19	(0.17 - 0.22)	77.8	(76.3 - 79.3)
Bronopol	0.14	(0.09 - 0.18)	77.1	(74.8 - 79.3)
III. RI < 0.0 (lower 95% CI)				
DMDM Hydantoin	0.01	(-0.06 - 0.08)	85.8	(82.4 - 89.3)
Sorbic acid	- 0.02	(-0.09 - 0.04)	85.9	(82.9 - 88.9)
Polyhexamethylene biguanide-HCl 2.5%	0.08	(-0.11 - 0.27)	78.3	(67.9 - 88.8)
Chlorhexidin digluconate	- 0.15	(-0.22 - - 0.09)	90.5	(87.5 - 93.5)
Paraben Mix	- 0.22	(-0.25 - - 0.19)	84.8	(83.1 - 86.5)
Iodopropinylbutyl carbamate	-	(-0.29 - -	84.6	(81.0 - 88.2)

	0.22	0.16)		
Triclosan	- 0.21	(-0.29 - - 0.13)	79.1	(74.1 - 84.1)
Sodium benzoate	- 0.23	(-0.29 - - 0.18)	92.2	(89.9 - 94.5)
Benzyl alcohol	- 0.23	(-0.31 - - 0.16)	76.0	(70.8 - 81.2)
Polyhexamethylene biguanide-HCl 5.0%	- 0.08	(-0.33 - 0.17)	73.3	(57.5 - 89.2)
2-Phenoxyethanol	- 0.44	(-0.65 - - 0.23)	85.0	(69.4 - 100.0)

Table 5: MOAHLFA Index

allergen	conc	M	O	A	H	L	F	A	Conspicuous characteristics
Allergens associated with occupational dermatitis in more than 20%									
Methylisothiazolinone	0.05	47.9	41	22.8	48	8.8	13	73	Occupational (and hand) dermatitis
(2-Phenoxyethanol) ¹⁾	1	70	40	25	45	15	10	75	
Quaternium 15	1	26.9	32	25.7	48	8	15.1	64.3	
Iodopropinylbutyl carbamate	0.2	46.3	31	23.4	46	13.6	10	76.6	
(Chloro)-Methylisothiazolinone (MCI/MI)	0.01	38.4	24	22.3	37	9.8	14.2	72.1	
Formaldehyde	1	36.9	24	21.4	36	10.9	13.8	69.1	
DMDM Hydantoin	2	38.1	23	22.4	39	12.4	13.9	67.5	Occupational (and hand) dermatitis and old age
Polyhexamethylene biguanid-HCl	2.5	46.7	28	13.3	38	13.3	15	85	
Methyldibromoglutaronitril	0.2	41.2	21	19.9	36	15.9	11.2	85.5	
Allergens associated with occupational dermatitis in less than 20%									
Sodium benzoate	5	50	19	30.3	29	13.1	14.8	57.2	male
Methyldibromoglutaronitril	0.3	43	19	15.8	33	14.2	13	79.8	hand dermatitis, male
Methyldibromoglutaronitril+PE	1	40.2	17	15.1	35	15	13.8	77.6	hand dermatitis, male
Sorbic acid	2	56.5	15	15.4	43	19.3	5.4	82.7	hand dermatitis, male, old age
Diazolidinyl urea	2	33	17	25.9	26	15.8	26.1	73.3	face dermatitis

Imidazolidinyl urea	2	33.6	16	27.1	24	17.7	27.3	69.9	face dermatitis
Bronopol	0.5	41.4	18	19.9	32	21.8	10.7	79.7	leg dermatitis
Chlorhexidindigluconate	0.5	46.2	16	23.9	21	23.9	17.9	75.3	leg dermatitis, male
Chloracetamid	0.2	28.5	15	14.9	25	30.5	12.6	82.7	leg dermatitis, women, old age
Paraben-Mix	16.0	45.9	11	15.0	22.8	28.6	10.2	76.1	leg dermatitis, male
Polyhexamethylene biguanid-HCl	5	36.7	10	16.7	30	13.3	16.7	76.7	unspecific
Triclosan	2	34.3	8.7	14.2	17	28.7	15	79.5	leg dermatitis
Benzyl alcohol	1	24.8	6.6	12.8	16	37.6	10.1	84.9	leg dermatitis, women, and old age
IVDK total (1996-2009)	.	37.4	15	17.8	27	10.9	15.2	66.4	

1) Caution: Confounding due to selection bias highly probable. In total, only 20 persons reacted positive, and 9/20 had occupations related to metal work

Fig 1: Time trends based on the bi-annual frequencies of sensitization to MDBGN in different concentrations, 1998 – 2004 as Euxyl K 400 (MDBGN 0.2% and phenoxyethanol 0.8%). In 2005 MDBGN 0,2% was tested in the monitor-series, in parallel with the baseline series. The decrease of MDBGN 0.2% and 0.3% was significant ($p < 0.0001$). The slight difference between both preparations in 2008/9 is not significant

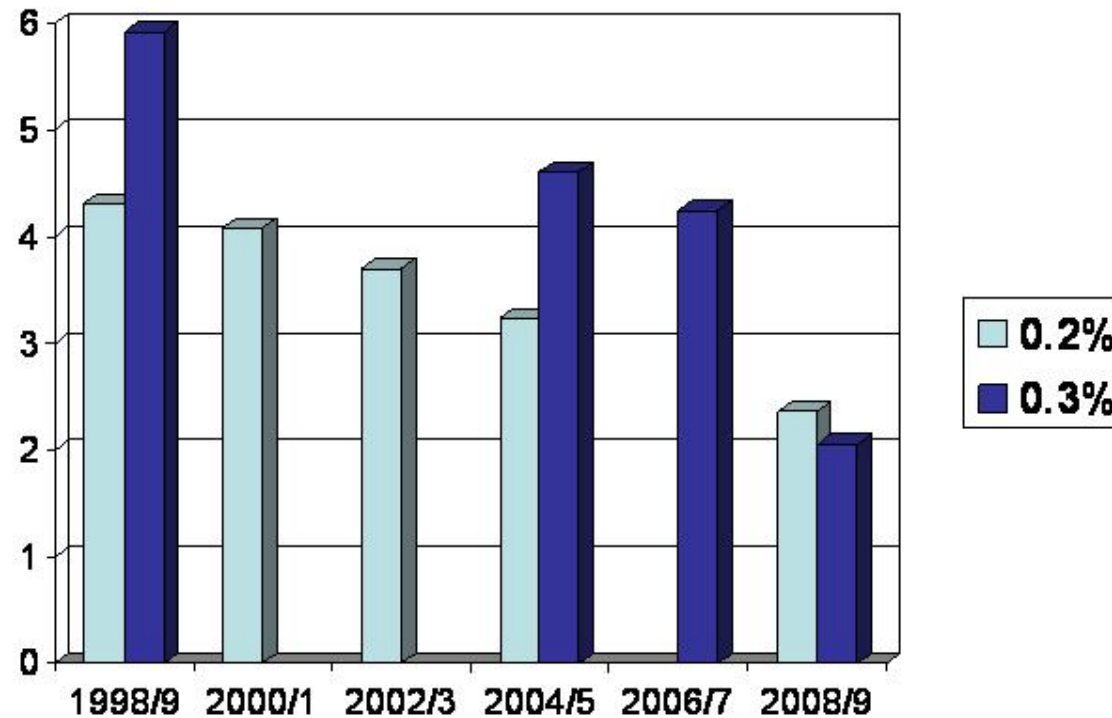


Fig 2 a: , Time trends based on the bi-annual frequencies of sensitization to halogenic preservatives and methylisothiazolinone (MI), standardized for sex and age. MI was tested 2005 in the monitor series, and regularly tested 2008/9 in the preservative and industrial biocide series.

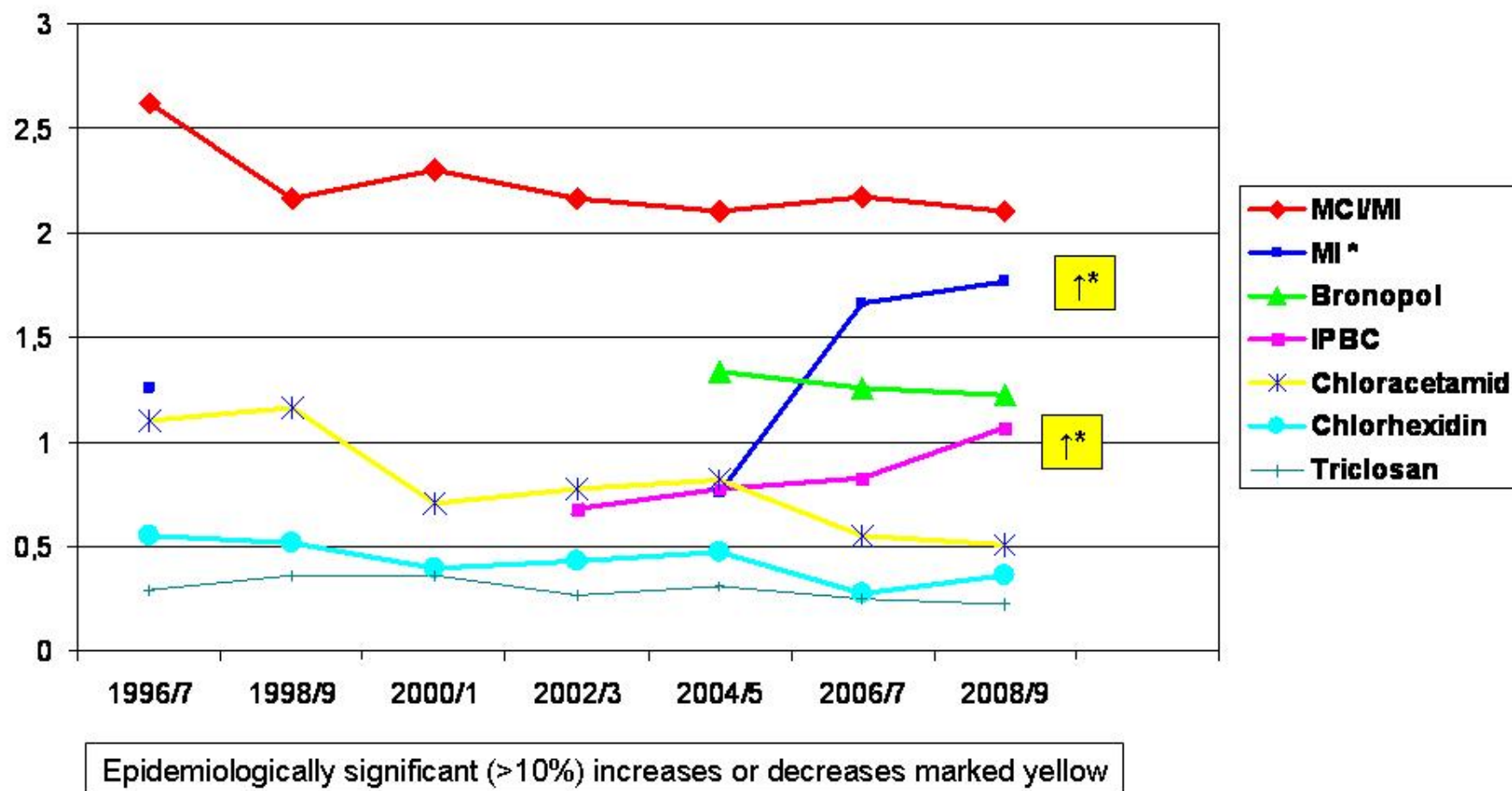


Fig 2 b: , Time trends based on the bi-annual frequencies of sensitization to formaldehyde and -releasers, standardized for sex and age.

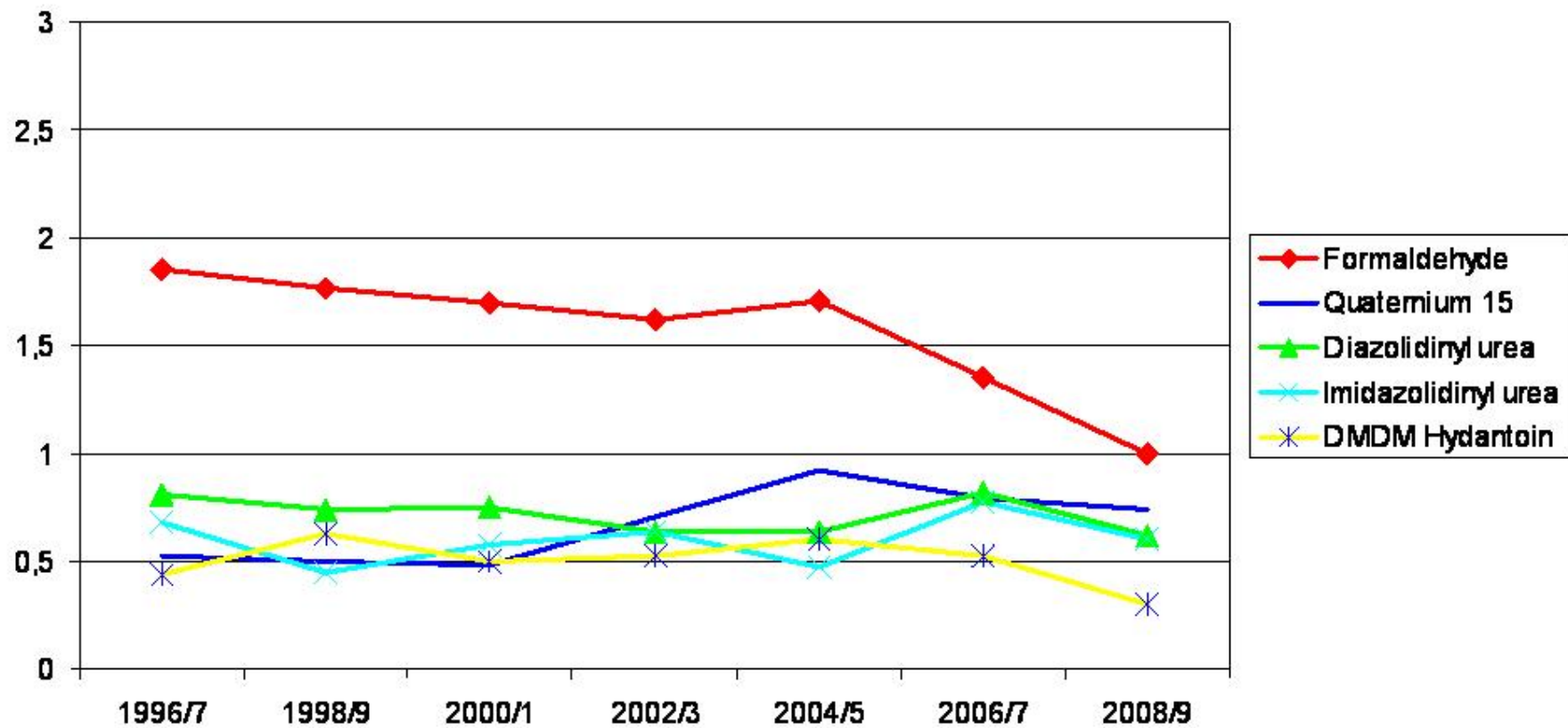
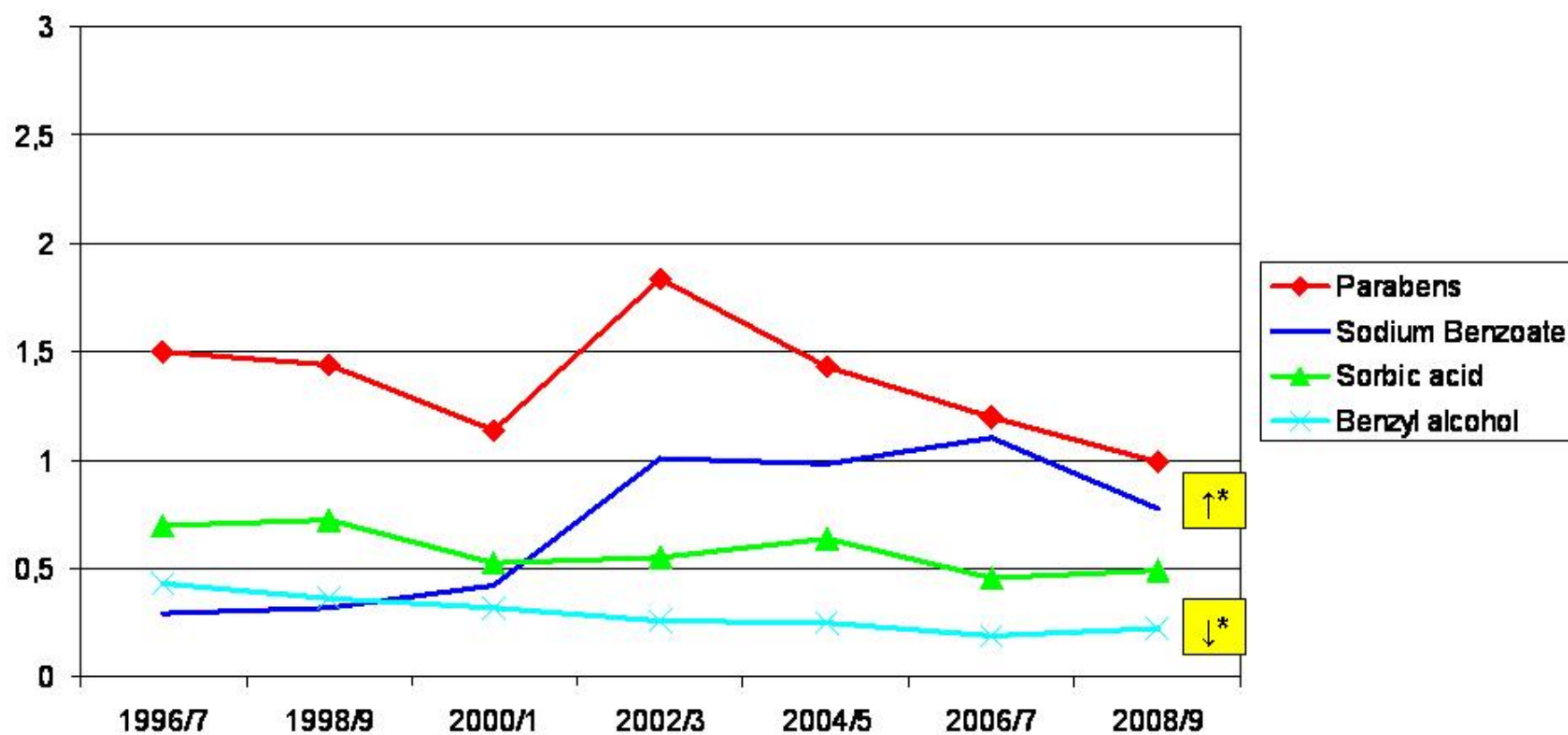


Fig 2 c: , Time trends based on the bi-annual frequencies of sensitization to benzene derivatives, standardized for sex and age.



Epidemiologically significant (>10%) increases or decreases marked yellow